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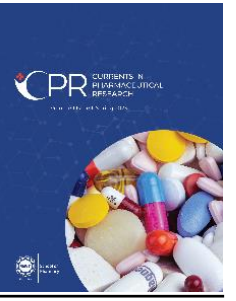

Title:	**Advancing Parkinson's Disease Treatment: Overcoming Blood-Brain Barrier Challenges with Polymeric Micelles**
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Advancing Parkinson's Disease Treatment: Overcoming Blood-Brain Barrier Challenges with Polymeric Micelles

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ABSTRACT

Pathophysiology of Parkinson's disease (PD) is characterized by significant barriers to effective pharmacotherapy, primarily due to the limitation of the intact blood-brain barrier (BBB), the rapid metabolism of drug substances in the body, and the low bioavailability of most drugs. Traditional treatments, such as levodopa and dopamine agonists, provide temporary symptomatic relief and have limited half-lives and peripheral side effects, as well as strongly inconsistent plasma concentrations. Such drawbacks have spurred interest in nanocarrier-based drug delivery systems, which could offer targeted, prolonged neurotherapeutic delivery to the central nervous system. Polymeric micelles (PMs) are considered versatile and are mainly used due to their nanoscale size, biocompatibility, adaptable core-shell structure, and ability to entrap hydrophobic and hydrophilic molecules. The current study focused on the design, development, and evaluation of PM-based delivery to PD (especially rotigotine-loaded micelles and multifunctional structures that simultaneously provide antioxidants or neuroprotective factors). Furthermore, the study described

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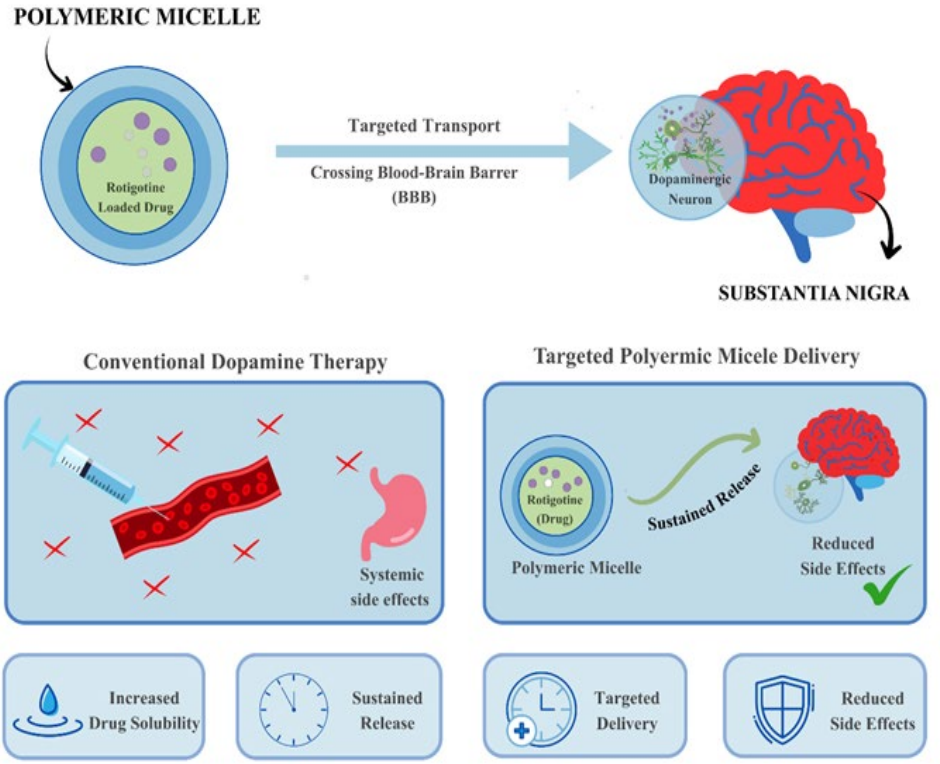
essential formulation approaches, including ligand-functionalized surfaces to target the BBB, pH- or redox-controlled drug release, and intranasal delivery. The study discussed these methods in terms of improving drug localization and extending the treatment's effects in the brain. Although pre-clinical research has demonstrated high potential, the clinical implementation of PM-based systems remains limited by scalability challenges, regulatory ambiguity, and limited availability of long-term safety data. However, when such difficulties are overcome through standardized characterization, stringent pharmacokinetic analysis, and improved approval pathways, PMs could be a viable solution for a sustained, targeted, and possibly disease-modifying treatment in PD.

Keywords: blood-brain-barrier (BBB), intranasal delivery, nanocarriers, neurodegeneration, Parkinson's Disease (PD), Polymeric micelles (PMs)

GRAPHICAL ABSTRACT



1.INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative condition that plagues about 3% of the elderly population, and is the second most common after Alzheimer's disease [1]. The illness results from the progressive degeneration of dopaminergic neurons in the substantia nigra, thereby affecting motor circuitry and reducing central dopamine levels. As such, bradykinesia, rigidity, and resting tremor are often observed in patients. Even though the exact etiology remains imprecise, there is a mounting body of evidence that the formation of alpha-synuclein and the disruption of cellular bioenergetics are central factors in the pathogenesis [2].

Levodopa is the main pharmacotherapeutic agent for PD. Still, its clinical use is limited by a short plasma half-life, poor aqueous solubility, and a tendency to cause dyskinesia and motor fluctuations due to intermittent dopamine delivery. In addition, the permeability of levodopa across the BBB is suboptimal, and systemic exposure can lead to adverse events, highlighting the need for more advanced delivery methods that provide sustained central nervous system exposure [3].

Metabolic breakdown of orally-taken levodopa, mainly by peripheral decarboxylation and aromatic L-aminooxy acid decarboxylase, limits central bioavailability to about 30% of the dose. Systemic effects, such as hypotension and nausea are caused by the peripheral conversion of levodopa to dopamine, which causes undesirable effects. Simultaneous administration with carbidopa is selective in inhibiting peripheral enzymatic activity, thus increasing cerebral levodopa levels. Nevertheless, motor variation (expressed as peak-dose dyskinesia) and interdose off periods persist in patients, usually 6 years after the start [3]. New methods, such as levodopa/carbidopa intestinal gel (LCIG) infusions are more predictable in terms of drug levels but involve surgically-invasive methods including gastrostomy, and so they may present another morbidity. The low solubility of levodopa also requires pH modification to enhance its pharmacokinetic action [4].

The complications are not present only with levodopa; it also indicates familiar difficulties with getting drug to reach the target and remain effective. New ways of delivering drugs need to be developed in order to overcome the types of drug access that cause drug release. A potential

avenue has been nanotechnology, especially Polymeric micelles (PMs). These micelles can increase drug solubility, stabilize drugs, and provide a means of trans-BBB delivery, potentially changing the manner in which PD is treated with more effective, localized therapy [4].

PMs are also emerging as a promising nanocarrier system for CNS drug delivery, offering stability, controlled release, and brain targeting. Surface-modifiable, biocompatible, and nanoscale therapeutics are highly soluble and are significantly enhanced in permeating the BBB. Since the existing PD treatment methods are mostly symptomatic, incorporating PMs would significantly increase treatment effectiveness while minimizing side effects. The current study discussed the pathophysiology of PD, the shortcomings of the current treatments, and how PMs can be used to change clinical outcomes [5].

2. PATHOPHYSIOLOGY OF PARKINSON'S DISEASE (PD)

Bradykinesia, tremors, stiffness, and cognitive decline are not the only symptoms of PD), complicated and neurological disorder may manifest in both motor and non-motor forms (motor and non-motor) [6]. Although the accumulation of alpha-synuclein (alpha-Syn) in the Lewy bodies has long been associated with the disease, there is growing evidence that other molecular mechanisms, especially the abnormalities of the tau protein, are also implicated in the pathogenesis of the disease [7].

2.1. Alpha -Synuclein Pathology and Tau Protein Pathology

The Braak stage is a model that forecasts the propagation of alpha-synuclein aggregates in the brain. This aggregation is caused by the disequilibrium between the formation and clearance of the alpha-synuclein, and it is commonly associated with SNCA gene mutation and defective lysosomal degradation [7].

2.2. Mitochondrial Dysfunction, Oxidative Stress, and Glutamate Excitotoxicity

One of the major causes of PD is mitochondrial dysfunction and oxidative stress that cause apoptosis, impaired energy generation, and elevated concentration of reactive oxygen species (ROS). This mitochondrial dysfunction is aggravated by the deposition of α -synuclein aggregates. Excitotoxicity is another determinant that is associated with

early neuronal damage and the elevated release of α -synuclein, and it takes place when excess glutamate is released, and calcium enters the cells [8].

The MAPT gene produces Tau protein, which is important in the control of axonal transport and the stability of the microtubules. However, under pathological conditions, Tau gets hyperphosphorylated, and this disrupts the ability of cells to perform some important functions, such as synaptic signaling and nucleocytoplasmic transport. Like α -synuclein, Tau is prion-like and may facilitate aggregation of both proteins, leading to a vicious cycle that speeds up neuronal degeneration. Although the results are inconsistent in diverse populations, genetic research has attributed the MAPT H1 haplotype to the risk of developing Parkinson's and cognitive impairment. Brain analyses conducted in the postmortem have demonstrated that the brains of PD patients harbor hyperphosphorylated Tau, which is usually co-located with α-synuclein in Lewy bodies, indicating a potential relationship between the two. Interestingly, the Tau pathology has also been detected in neural grafts placed in PD patients, which begs the question that Tau may also propagate similarly to prions [9].

Tau levels are being studied in cerebrospinal fluid (CSF), including total Tau (t -Tau) and phosphorylated Tau (p -Tau), as biomarkers of cognitive impairment and PD progression. High levels of Tau have been linked to dementia and may be used to help differentiate between tremor-dominant and non-tremor-dominant types of PD, which may result in more tailored treatment approaches [9].

Findings of the experiments involving mouse models with modified Tau levels are not completely congruent. Some studies posit that lowering Tau levels can be used to relieve the symptoms of PD. Otherwise, iron accumulation and impaired autophagy are not accompanied by any apparent benefits or even detrimental effects of Tau deletion. Since Tau has a significant role in normal and pathological neuronal functions, it is a very important target of development in therapy. Nevertheless, the role of Tau and its possible use in the treatment of PD require more studies [10].

2.3. Genetic Factors and Molecular Targets

Recent developments in the research of molecular pathology have provided various treatment options for PD. Lewy bodies, which are the hallmark of the pathogenesis of PD, are formed in the cells due to the accumulation of alpha -synuclein (alpha -Syn), which makes it an important

research object. The inhibitors of aggregation and the promoters of autophagy and antisense oligonucleotides can be used to decrease its toxicity, and in the early models, they all have shown a chance of being used as a treatment. Originally discovered in relation to Alzheimer's disease, Tau is now being studied in the context of cognitive impairment related to PD. Tau has emerged as a target for inhibiting Tau kinases, including GSK-3β and other therapies targeting Tau, to ameliorate symptoms of tauopathies [11].

Mitochondrial dysfunction and oxidative damage are the leading causes of PD that help to degenerate the nerve cells. In order to reverse these effects, scientists are exploring the use of Nrf2 activators, CoQ10, and MitoQ as possible ways of preventing damage done to neurons and slowing down the progression of the disease. The purpose of these compounds is to improve the mitochondrial activity and minimize the oxidative stress to provide a promising solution towards neuroprotective therapy in PD [12]. The processes of neurodegeneration in such diseases as Parkinson's involve the dysfunction of the autophagy-lysosome system, which takes care of the clearance of damaged cells and proteins. Owing to this, drugs, such as ambroxol and rapamycin that are capable of enhancing autophagy, are undergoing preclinical trials as possible drugs. They can be used to enhance clearance of toxic proteins, which is a promising way of controlling or delaying the development of neurodegenerative diseases [13]. Re-purposed drugs, such as amantadine are under investigation to address glutamate excitotoxicity, which is excess NMDA receptor activity resulting in neuronal damage. The antiviral Amantadine, also in the treatment of the symptoms of Parkinsonism, has been found to have potential in curbing this excitotoxicity by regulating the activity of glutamate. This method can be used to preserve the neurons and enhance the results in disorders, such as PD [14]. Kinase inhibitors and gene-silencing methods are becoming promising targeted therapies for genetic variants of genes associated with PD, including LRRK2 and MAPT genes. These methods seek to directly alter the underlying genetic reasons, which could provide an opportunity for more customized treatment. On top of that, research has also made certain discoveries, including biomarkers, such as cerebrospinal fluid (CSF) Tau and A24 levels, which can be used to diagnose PD earlier and specifically treat individual patients, thus improving outcomes [15].

3. CHALLENGES IN PARKINSON'S DISEASE (PD) DRUG DELIVERY

Levodopa, the most commonly used to prevent peripheral metabolic degradation as the combination with carbidopa, is the most effective pharmacotherapeutic intervention for PD. Levodopa suppresses motor manifestations, such as tremor and rigidity by restoring dopaminergic tone in the central dopaminergic system. However, chronic levodopa exposure triggers motor complications, such as levodopa-induced dyskinesias and wearing-off phenomenon. This significantly decreases levodopa therapeutic index, thus undermining the health-related quality of life of patients [16].

Recent studies have clarified that these motor complications arise as a function of the pharmacokinetic profile of levodopa uptake at the nigrostriatal dopamine receptors. According to the previous studies, levodopa penetrates the central nervous system, not in constant flux, but in discontinuous bursts, causing a heterogeneous stimulation of the receptors. This unequal exposure to dopaminergic is postulated to develop motor impairment. In addition, it is empirically proven that there is a dose-dependent relationship between the administration of levodopa and the occurrence of dyskinesias. The chronic adverse outcome experienced in patients can be attributed to these pharmacodynamics and pharmacokinetic interactions [17].

3.1. Overcoming the Blood-Brain-Barrier (BBB) for Pulsatile Receptor Activation

The BBB is an extremely restrictive, tightly controlled interface that hinders pharmacologic interaction and approach of the CNS in PD. The BBB protects the neural tissue against neurotoxins due to its ability to attenuate permeability. However, it also tends to inhibit the efficacy of treatment against dopaminergic receptors located in the substantia nigra due to its restrictive quality [18]. Though levodopa crosses the BBB due to its lipophilic qualities, its movement is differentiated by periodic bursts with activation of dopamine receptors and produces irregular dopaminergic signaling, which may cause dyskinesia. The violation of the integrity of BBB can also take place and support the intrusion of therapeutic molecules but it also exposes the brain to external neurotoxins. One postulates that changes in the BBBs assist in the advanced pathology of PD, thus making it difficult to provide therapy. To curb such challenges, various measures

have been worked out [19]. These can be in the form of one method using genetically engineered nanocarriers that have particular ligands and antibodies, and thus allow receptor-mediated transcytosis across the barrier. The other method involves the use of the low-intensity focused ultrasound (FUS) to temporarily open the BBB, allowing delivery of drugs at a spatial locality. However, still, there are concerns that have not been fully resolved. These include the strength of these methods, the safety of long-term application, and the ability to control the accurate regulation of the release of drugs, which restrict the clinical practice [20].

3.2. Non-specific Distribution and Systemic Side Effects

The main shortcoming of modern pharmacotherapies of PD is that they are distributed non-specifically, leading to massive general systemic toxicity. Subsequently, systems of delivering drugs that target specific areas of the brain have become a subject of interest. Such methods increase exposure to access-focused cerebral regions, thus optimizing the therapeutic efficacy and minimizing off-target toxicity. The BBB plays a crucial role in neuroprotection immune to external insults of the brain, but, conversely, inhibits the diffusion of therapeutic agents across pathology foci; hence, a significant hindrance to the treatment of central nervous system maladies. This is worsened by the fact that efflux transporters are more active in the disease condition. Recent literature highlights the potential of adjunctive modalities, including focused ultrasound and nanocarrier technologies, to enable the BBB penetration and enhance drug delivery, which enhances the therapeutic effects of PD and other neurodegenerative diseases [21, 22].

4. POLYMERIC MICELLES (PMS): PROSPECTIVE DRUG DELIVERY SYSTEM

PMs are increasingly discussed as an extremely effective nanocarrier system to improve the delivery of drugs in the field of PD. Thus, this helps overcome major drawbacks of the currently existing therapeutics, such as deficient bioavailability, systemic adverse effects, and unstable dopamine levels [23].

This flowchart is a summary of the usage of polymeric nanoparticles to deliver drugs in Parkinson's. It categorizes them on the basis of their origin (natural and synthetic polymers), therapeutic actions (dopaminergic and other targets), and research techniques (in vitro models and in vivo routes of administration). This paradigm presents the malleability of polymeric

nanoparticles in enhancing controlled medication delivery and solving issues in the treatment of PD.

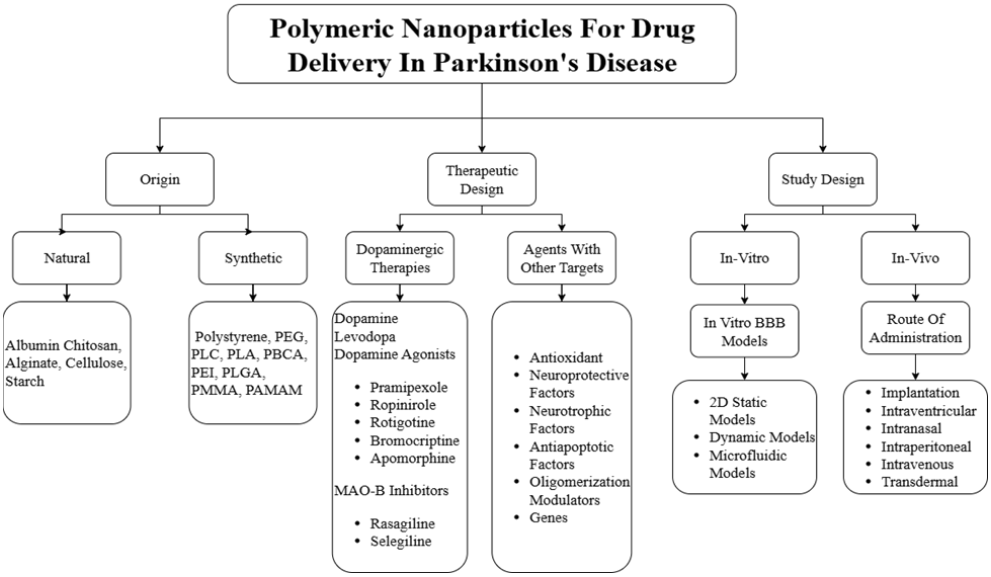


Figure 1. Polymeric Nanocarriers for the Treatment of Parkinson's Disease (PD) [22]

4.1 Structure and Self-assembly of PMs

Structure and Self-assembly of PMs consisting of polymer backbones forming crossovers to generate hydrogel structures called crosslinked PMs or to create linkers that form crosslinked PMs by connecting them into a hydrogel structure named crosslinked PMs.

Amphiphilic copolymer-based micelles can be produced by self-assembly [24], with an inside comprising a hydrophobic core, which entraps and stabilizes pharmaceuticals that are not soluble in aqueous solution, and an outside coating which overcomes solubility obstacles, lengthens its circulation duration, and protects the drug against early degradation. To get its way across the BBB, PMs may be modified or coated with ligands or antibodies to be labeled as a target [25]. It uses the Enhanced Permeation and Retention (EPR) effect to induce desired cytosis at inflamed neuronal locations. Moreover, micelles may also be designed as pH-responsive to be released in the gastrointestinal tract upon dissolution, or be mucoadhesive, and thus, become more interactive with the intestinal mucosa and be

absorbed. They are non-toxic and biodegradable, making them ideal to be used in the treatment of chronic and long-term PD [26].

4.2. Drug Encapsulation and Release Mechanism

The therapeutic success of PMs largely depends on how the formulations are designed, as they determine the degree of drug loading, the release processes, the biodistribution, and the stability of the micelles. The self-assembly of PMs in aqueous media is made of an amphiphilic block copolymer to form a hydrophobic core, which entraps lipophilic drugs and a hydrophilic corona, forming a soluble that is sterically-stabilized. Some of the common hydrophilic segments used include polyethylene glycol (PEG), whilst the hydrophobic segments include polylactic acid (PLA), polycaprolactone (PCL), or poly (lactic-co-glycolic acid) (PLGA). The hydrophilic/hydrophobic ratio (ideally 3: 7 to 8: 2) affects the formation of the micelles, the drug entrapment efficiency, and the controlled release properties [27].

Depending on the physicochemical characteristics of the drug, there is a selection of a micelle preparation method. The least complex method is the direct dissolution, which applies to moderately hydrophobic compounds but is applicable only to a restricted scope. Dialysis is viewed as ideal in attaining uniform sizes of the microscales and high efficiency of encapsulation of the drug, especially for the heat-sensitive compounds. The thin-film hydration technique is often used when a drug that is less soluble in water needs to be controlled concerning micelle size. A modified solvent-dispersion method is the preferred choice with delicate substances that require exceptionally gentle treatment, with water-soluble solvents being used to bring about the creation of micelles at low temperatures [28].

The incorporation of drugs can be done either by physical (hydrophobic interactions) or chemical (drug-polymer conjugates), and the position of the drug can either be core or interface, and hence may influence bioavailability. Linkers (or targets) can be engineered with cross-linking or stimuli-reactive (e.g., pH- or redox-sensitive) linkers to improve the stability of medications and provide targeted release [29].

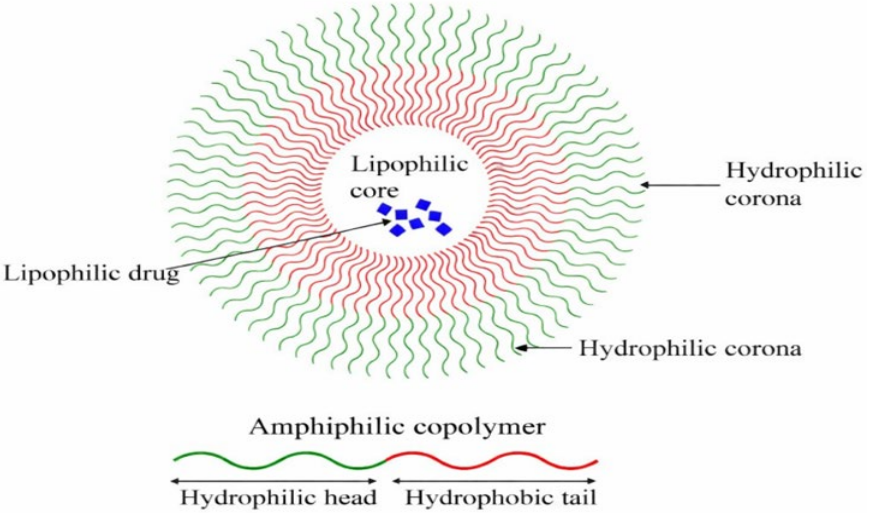


Figure 2. Schematic Representation of an Amphiphilic Copolymer Micelle for Drug Delivery [27]

Micelles are hydrophilic corona (justified as green heads) and lipophilic (hydrophobic) cores (justified as red tails), which are a result of the spontaneous self-assembly of amphiphilic copolymers. The lipophilic therapeutic agent is entrapped in the oleophilic core, and the oleophilic corona is the one providing colloidal stability in aqueous micelles.

Critical Micelle Concentration (CMC) is also an important parameter of optimization; a small CMC allows the solution to remain stable when it interacts with biological fluids, such as blood. Active targeting by the ligand folic acid or transferrin can be used to achieve surface functionalization, which increases precision and reduces off-target effects. These targeted PMs have significant potential in safe, sustained delivery, and targeting, especially in neuro-oncological and neurodegenerative disorders, such as PD [29].

4.3. Development of Conventional PMs to Advanced Nanocarrier Systems in PD

PMs, which are considered as one of the widely studied nanocarrier systems in the treatment of PD, have the merits of hydrophobic solubilization of drugs, prolonged circulatory retention, and pharmacokinetic characteristics. Amphiphilic block copolymer-derived micelles have been reported to stabilize dopamine and levodopa in

protecting them against early catabolism and metabolic inactivation, thereby increasing treatment effect. The polyethylene glycol (PEGylation) or glutathione (GSH)-coated variants also show further enhancement concerning BBB permeation, creating a way of translocating therapeutic agents to neuronal substrates efficiently [29].

In addition to the traditional micellar systems, new studies have examined complex alterations to overcome oxidative stress and meet poor therapeutic responsiveness. By way of example, co-delivery micelle assemblies with curcumin and levodopa have demonstrated synergistic neuroprotective actions, where curcumin lowered the effects of oxidative-stress and rescued levodopa-related side-effects [29]. To achieve spatially and temporally specific drug delivery in the cerebral microenvironment, smart PMs that have been designed to contain pH or redox-responsive triggers, have been developed [30].

Recent developments in the use of DNA-based nanocarriers, especially polymeric DNA nanocarriers, have enhanced the effectiveness of micellar delivery strategies in the treatment of disease. The carriers allow one to perform gene-targeted interventions by silencing the pathogenic or up-regulating protective genes, thus offering customized delivery with maximum potency and minimum toxicity when used in conjunction with functional polymers [29]. These types of gene-delivery platforms represent the shift of micellar-based approaches to nano-carriers, which can serve multiple functions and regulate the progression of PD [30].

All the aspects mentioned above highlight the necessity of conventional micelles to PD pharmacotherapy, and the progress to functionalized, stimuli-responsive, as well as gene-based nanocarriers adds significantly to their flexibility and targeting properties as therapeutic platforms.

4.4. Reason for Directing Intention on Polymeric Micelles (PMs)

Current PD pharmacotherapies, levodopa and dopamine agonists, have reduced plasma half-lives, widespread extrapyramidal metabolism, unselective cerebral localization, and insufficiently optimal solubility, thus triggering motor instability and systemic toxicity. It is against these limitations that PMs are the focus of this review, as they exist to mitigate these limitations by improving the solubility of levodopa and dopamine agonists, prolonging their circulation and protecting them against early degradation.

PEGylated or glutathione-coated micelles can be used to permeabilize the BBB but stimuli-responsive micelles can be used to release drugs in controlled amounts depending on cerebral pH changes or oxidative events. These properties confer a significant benefit relative to traditional therapeutics, in which the normal effects are mainly to provide symptom relief with no effects on the progression of the disease.

Nucleic acid therapeutics as well as small molecule therapy, such as levodopa or rotigotine, can be encapsulated into micellar systems and thereby may alter the pathology of the disease, other than just alleviating symptoms. Uniquely, PMs combine both pharmacological and genetic modalities into the same platform, unlike other nanocarriers, such as oral agents. This versatility of use is characteristic of how promising they are as new therapeutic modalities to treat Parkinsonism.

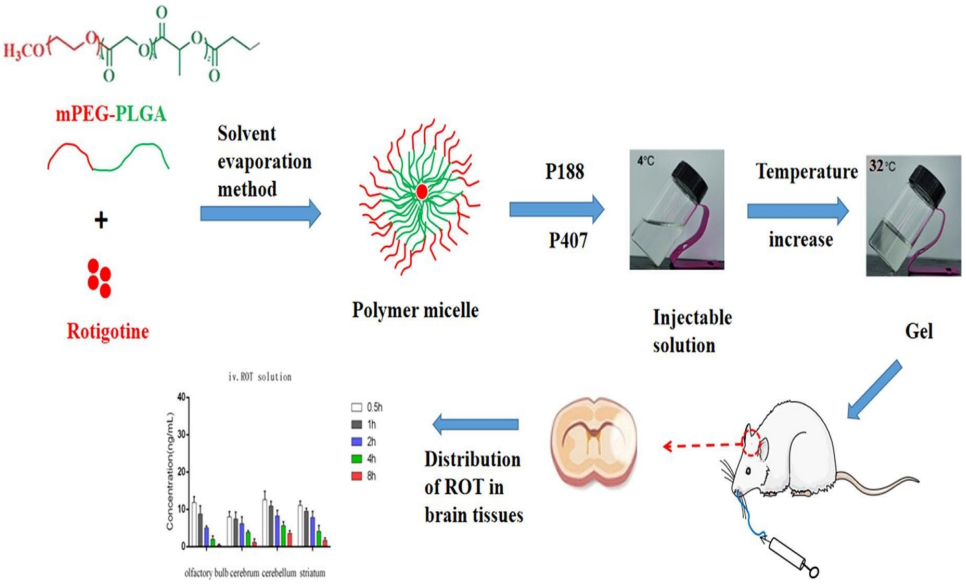


Figure 3. Schematic Apparatus of a Thermosensitive Injectable Micelle-gel System of Rotigotine Brain Delivery [32]

Rotigotine Polymeric Micelles (PMs): To develop polymeric microgel-based products, a chemical route was adopted, with polymeric microgels being the desired product type.

Rotigotine is a non-ergoline dopamine agonist used in the treatment of Parkinsonism and restless-leg syndrome, which is characterized by therapeutic utility and is marred by its very low water solubility, intense

first-pass metabolism, and limited cerebral penetration. To address this, PMs have been designed as a viable nanocarrier platform of rotigotine through the deployment of their core -shell architecture to enhance aqueous solubility and support extended drug release [31].

Rotigotine-loaded micelles were made by utilizing the mPEG -PLGA copolymer through solvent evaporation. The micelles were introduced into a thermosensitive gel system that was subjected to the sol, relating to the injectable solution at 4°C and the gel at 32°C. The system improved the distribution of rotigotine in the specific brain tissues following the intranasal administration in rats.

This is because the most common method of preparing PMs is by the solvent evaporation or dialysis method. In this protocol, rotigotine in combination with amphiphilic polymer, that is, mPEGplag or poloxamer is dissolved in an organic solvent and then dropwise into a water medium is added under constant stirring. This self-assembly causes the spontaneous appearance of nanosized micelles and the removal of these micelles out of the organic phase by a decrease in the system pressure. Before utilization, the resulting product would be normally filtered and lyophilized [31].

The shells of rotigotine made using mPEG PLGA had a mean hydrodynamic diameter of 88.6 +1.5nm, an encapsulation efficiency of 93.5 +0.8%, and a drug loading percentage of 19.9 +0.6% in one particular research. These micelles were then added into a thermosensitive in-situ gel that consisted of 22% poloxamer 407 and 2% poloxamer 188. The resulting formulation gelled at about 32.3 o C and had a nasal-compatible pH [31].

The release studies *in vitro* showed sustained release of up to 48 hours, with a release percentage of approximately 53% of rotigotine being released out of the gel meshwork and 75% of rotigotine being released out of the micellar preparation. Dosing frequency can be minimized and may improve patient compliance with such a controlled release profile [33].

In vivo pharmacokinetic studies demonstrated that cerebral targeting greatly increased with intranasal delivery of the micellar gel [34]. Rotigotine was found to be significantly higher in the olfactory bulb, cerebrum, cerebellum, and striatum as compared to the levels found when it was delivered intravenously. Meanwhile, the mean residence time (MRT) increased, hence representing long-term systemic exposure and increased therapeutic efficacy [33].

Therefore, the idea to encapsulate rotigotine into polymeric vesicles, especially in combination with thermosensitive gels, is an attractive approach that can be used to improve the nasal cerebral delivery of rotigotine as well as to avoid the constraints of the conventional formulations [34].

5. METHODOLOGY

The literature review presented in the current study is an attempt to synthesize and critically analyze new trends in the use of PMs to deliver drugs in order to treat PD. It was done systematically to achieve exhaustive coverage of relevant literature, and is a way of validating the reliability of the results.

5.1. Inclusion and Exclusion Criteria

The existing review included researches published within January 2020 up to June 2025 and in English that reported an innovative scientific or clinical evidence on polymeric micelle-based drug delivery approaches to PD or closely-related neurodegenerative paradigms. Selected studies were characterized in terms of the type of polymer used, the encapsulation methods of various drugs, the kinetics of their release, their distribution in the body, and their therapeutic effects.

Articles on review, abstracts of conferences, editorials, and studies based on non-polymeric carriers (e.g., liposomes, dendrimers, or metallic nanoparticles) were excluded, unless used in contextual comparison. The studies relevant to PD or to the dopaminergic neurodegeneration were considered.

5.2. Study Selection and Data Extraction

Titles and abstracts were filtered by two independent reviewers as pertinent, and subsequently full evaluation of selected publications was done exhaustively. Issues of disagreement were solved via consultation in order to reach an agreement. Isolated critical information included: polymer type and micelle formulation methodology; drug or bioactive agent encapsulated; particle properties; dimensions, surface charge, and morphology; drug loading capacity and encapsulation efficiency; release profile and stability data, and *in vivo* and *in vitro* models, for instance pharmacokinetic, biodistribution, and therapeutic results.

Table 1. Preclinical and Clinical Studies on Polymeric Micelles

Micelle System	Drug/Cargo	Model (Cell/Animal)	Route	Key Findings	Study Type
PEG–based micelles	Poorly soluble drugs	*In vitro* assays	Oral/IV (review of experimental data)	Improved solubility and bioavailability	Preclinical study
PEG–PCL micelles	Anticancer agents	Rats/mice	Oral	Enhanced oral absorption and stability	Preclinical study
Various polymeric micelles	Multiple hydrophobic drugs	*In vitro/in vivo*	IV	Better stability, reduced toxicity	Preclinical study
Different micelle formulations	Anticancer & CNS drugs	*In vitro* and animal	Multiple	Reported improved drug loading, controlled release	Preclinical study
Thermosensitive polymer micelles (rotigotine)	Rotigotine	Rats	Intranasal (nose-to-brain)	Enhanced brain delivery and sustained release	Preclinical study
Lecithin–chitosan micelles	Rotigotine	Rats	Intranasal	Superior brain targeting vs. plain drug	Preclinical study
Nanomedicine review, including micelles	Multiple	Translational overview	Oncology/CNS	Discusses hurdles to clinical translation of micelles	Clinical study
Translational framework for nanomedicines	Multiple	Conceptual framework	Oncology/neuro	This framework provides a roadmap for bringing micelles to clinical applications	Clinical study
Regulatory aspects	Nanomedicines incl. micelles	Regulatory/preclinical	–	Highlight safety, risk-based approaches	Clinical study
PEG–PCL micelles	Doxorubicin, paclitaxel	Clinical (reported in review)	Cancer	Some formulations entered Phase I/II but had limited success	Clinical study

5.3. Data Synthesis

The methodology used was a narrative synthesis to rationalize and compare the findings of the various studies with a focus on identifying recurring trends, innovations, and limitations.

The data were coded by polymer type, therapeutic agent, and route of administration where appropriate. Literature gaps were also identified to guide future research directions.

6. LIMITATIONS AND FUTURE PERSPECTIVES

6.1. Problems in Clinical Translation

A breakthrough has already been realized in the polymeric micelle (PM) technology; however, some serious challenges hinder the use of these developments in regular clinical practice, especially when it comes to curing PD. Despite the significant potential offered by PMs in improving drug solubility, targeted delivery, and controlled delivery of the drug, the task of scaling up the manufacturing is an effective impediment to successful distribution.

6.2. Problems with Production and Scale-up

Many parameters, including particle size, morphology, drug loading efficiency, as well as biodegradability, are carefully controlled to guarantee the reliable synthesis of PMs, which respond predictably to physiological cues, for instance pH, redox potential, or temperature. These are essential variables in the consideration of not only safety but are also crucial to the therapeutic efficacy of human purposes. The regulatory environment of nanomedicines keeps changing, hence posing even more uncertainty in the clinical trial design and conduct.

Although intranasal application may be an appealing method of bypassing the BBB, its effectiveness in human beings has not been confirmed. The majority of preclinical studies have been limited to rodent models, which are not a complete reflection of the complexity of human nasal and cerebral anatomy. It follows that translation of these therapies into the human body is complicated by interspecies anatomy and pharmacokinetics. Another technical issue that is complicated by a lack of complete data on long-term pharmacodynamics, biodistribution, and possible chronic toxicity is the development of delivery devices that are anatomically compatible with human physiology [35].

6.3. Nanomedicine Regulatory Issues

The logical way forward in altering disease progression, with respect to dopaminergic neurons, is the introduction of DNA-based polymeric nanocarriers that are engineered to release nucleic acid therapeutics (that is, siRNA or plasmids) into the cell. However, difficulties, such as the inherent sensitivity of genetic material, potential off-target effects, and a lack of clinically valid vectors are major obstacles to clinical implementation. Unresolved problems include safety, immunogenicity, and the guarantee of reproducible gene expression, as they require additional research [36, 37].

To deal with these challenges, a multifaceted approach is required with the inclusion of multicenter, randomized controlled trials to be able to validate both safety and efficacy. It is recommended to use the animal models that are more physiologically similar to humans, that is, marmosets. Concurrently, optimization of the formulations to improve biocompatibility and retention, as well as creation of strict regulatory policies in regard to gene-based nanocarriers would be necessary. Commercialization must not be done prematurely until there is considerable clinical confirmation [38].

After strategically addressing scientific and regulatory challenges, the next generation of therapeutics addressing PD and other neurodegenerative diseases, PMs, such as DNA nanocarriers, might become the powerful solutions of the future [39].

6.4. Limitations

Although there has been significant progress in the development of PMs used as targeted drug delivery systems in neurodegenerative diseases, the usage of PMs in PD is still in its initial translational stage. The existing literature is mainly based on evidence of concepts, which, in many cases are limited and have been done *in vivo* or few animal models, with minimal clinical evidence used in assessing treatment efficacy and safety in human participants.

The primary disadvantage is that the knowledge of the micelleneurobiology interactions is inadequate in terms of long-term biodistribution and BBB entry mechanisms, as well as in terms of clearance. Even though different formulations portray the desirable drug-loading and controlled-release properties, tuning of physicochemical parameters, specifically when the dopaminergic neurons need to be targeted, namely the micelle size, surface charge, and polymer composition, is lacking.

Besides, most studies evaluate single-agent delivery systems, and pathogenesis of PD involves multifactorial pathways, including but not limited to oxidative stress, mitochondrial failure, and protein aggregation. This highlights the lack of development of multi-drug/functional micelles that can deliver combination drugs or may accommodate functional diagnostic imaging components.

Translational-wise, the lack of standardized *in-vivo* test methods poses the problem of cross-studies comparison. The lack of consistency in the animal models, dosing regimens, and outcome measures also contributes to the hindrance of the generation of credible preclinical studies. There is also a lack of regulatory considerations in relation to PMs in the neurological application, and, consequently, there has been no willingness to investigate this issue sufficiently already. This may lead towards uncertainty in the context of clinical approval procedures.

To eliminate these shortcomings, there is a need to systematically enhance the design of the micelles to target these PD displays. Complex *in-vivo* studies addressing long-term safety testing and pharmacokinetic studies would be conducted. These multifunctional systems, delivering to governments and medical facilities in real-time, need to be reviewed. Preclinical methods should be standardized to improve their reproducibility and make them easily translatable. It is important to fill these research gaps and ensure that PMs are developed to create clinically-viable nanotherapeutic agents in order to cure PD.

7. CONCLUSION

PD is a progressive and chronic disorder that affects the function of the brain. Presently, it is treated with levodopa, however, it is poorly-bioavailable and has systemic side effects. Therefore, these treatments mainly have the effect of providing relief from symptoms rather than improving outcomes for the underlying cause of PD. These difficulties relate at least in part to the fact that all of the current therapies for PD do not readily cross the BBB. PMs are being explored as nanocarriers that can improve solubility, extend release, and enhance brain targeting of PD therapies in studies with animals. These PMs may have either pH-sensitive or ligand-based delivery systems, possibly making them an effective means of delivering PD therapies to the brain. There is currently limited evidence showing their effectiveness when delivered in trials with human subjects.

There are many challenges to bringing a PM system into clinical use, including the challenges of determining stability, safety, toxicity, immune response, biodistribution, large-scale production, and regulatory approval. PMs should be viewed as experimental systems that would require additional optimization and a rigorous evaluation of their safety and pharmacokinetics before they are used clinically.

Author Contribution

Mohammad Affan Mahmood: conceptualization, writing – review & editing. **Muhammad Ali:** supervision, project administration. **Namirah Islam:** methodology, writing - original draft. **Amima Naz:** writing - original draft. **Aziza Ahmad:** writing – review & editing. **Shabana Naz Shah:** methodology, writing – review and editing. **Hajira Kanwal:** visualization, writing - original draft. **Laiba Khan:** software, writing - original draft.

Conflict of Interest

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

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